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The HIV vaccine saga

Kendall A Smith*

Address: The Division of Immunology, Department of Medicine, Weill Medical College, Cornell University, New York, NY 10021, USA

Email: Kendall A Smith* - kasmith@med.cornell.edu

* Corresponding author

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Abstract

The development of a vaccine that can prevent infection by the Human immunodeficiency virus or prevent the Acquired Immunodeficiency Syndrome has remained elusive despite 20 years of scientific effort. This "Commentary" analyzes the reasons that the development of a vaccine has been so difficult, and proposes a plan to work towards an immunological approach to investigate the best vaccine candidates in the first world in individuals who are already infected, before taking the most promising vaccines to the developing world to attempt to prevent infection and disease.

SAGA: (Old Norse) "a long, continued heroic story that is action-packed, but not especially romantic, and that is historical or legendary or both".

Introduction

In 1984, Margaret Heckler, then Secretary of Health, Education and Welfare, called a press conference and announced that Robert Gallo of the National Cancer Institute had discovered the virus responsible for causing the Acquired Immunodeficiency Syndrome (AIDS). Gallo then predicted that a vaccine for this dread affliction would soon be in hand, certainly within two years. However, years passed, until in 1997 President Clinton declared, "an HIV vaccine would be developed in a decade's time". Subsequently, in his State of the Union Address, 2003, President Bush stated that he is now going to ask Congress to appropriate $15 billion to combat the spreading HIV epidemic in Africa and the Caribbean, and an AIDS vaccine still is nowhere in sight.

Twenty years after the discovery of the AIDS virus, now known as the Human Immunodeficiency Virus (HIV), we know that HIV was actually first isolated and reported in 1983 by a team from the Pasteur Institute lead by Luc Montagnier, and that Gallo's group had simply re-isolated the same virus that the French team had sent to them a year earlier, thereby confirming the veracity of the original isolate and solidifying the putative cause of AIDS as due to a new retrovirus [1,2]. Moreover, despite a huge amount of money directed to basic and clinical science since that time, a vaccine that can prevent infection by HIV remains elusive. If this has not been a "saga" there never was one. But why has the development of an HIV vaccine been so difficult, and is there no end in sight?

Some of the answers to these simple questions reside in the history of immunology, which was detailed by my editorial entitled "Medical Immunology: A New Journal for a New Subspecialty" [3]. We really have not understood what actually constitutes a successful vaccine, despite the more than two centuries that have elapsed since Sir Edward Jenner described the first effective vaccine for smallpox virus in 1798 [4]. Consequently, all of the vaccines currently in use were developed empirically, and only within the past 50 years, without a comprehensive understanding as to how the immune system functions.

Now we are confronted with the worst pandemic in history, a pandemic that threatens to unravel societies around the world, just at the time that we have all become inter-

dependent in a "global economy". Accordingly, the search for an effective HIV vaccine is perhaps the most important scientific challenge of our generation, if not the most crucial ever in the history of science. Therefore, at this juncture it is imperative to detail the progress and the prospects in the quest.

Discussion

Subunit Vaccines and Neutralizing Antibodies

Initially, it was thought that a subunit vaccine, constructed from the viral envelope protein, could be rapidly and efficiently developed using the modern techniques available through genetic engineering. It was thought that immunization with the viral envelope glycoprotein, gp120, should generate neutralizing antibodies that would prevent infection, thereby yielding protective immunity. Of course, this was the traditional approach to vaccine development from the '50s. Successful immunization was tested by monitoring for serum neutralization of viral infectivity *in vitro*. However, unbeknownst to these earliest AIDS vaccine investigators, it turns out that HIV had already evolved very complex ways to evade antibodies that bind to the distinct areas of the viral envelope molecules where they interact with the cell surface virus receptors. Therefore, neutralizing antibodies are very difficult to generate, either after natural infection or immunization.

The viral envelope molecules are heavily glycosylated, and the large carbohydrate molecules serve to mask potential protein epitopes, as well as hinder antibody binding even if such antibodies are generated. In addition, the envelope molecules are expressed as trimers, which very rapidly undergo marked conformational changes upon contact with the viral cell surface receptors, CD4 and CCR5/CXCR4 [5]. These conformational changes occur so rapidly that the transition state is only open to immune recognition briefly. Consequently, investigators are now trying to generate stable trimeric gp120/gp41 molecules that can be used as immunogens, which will stimulate antibodies that can compete for the binding sites on the cell surface receptor molecules. Although a great deal of progress has been made [6,7], this "holy grail" of HIV immunology still is not within reach.

Antigen Processing and Presentation to T Lymphocytes (T cells)

At the time that HIV was discovered in 1983 [8], immunologists were just beginning to unravel the complex processes of antigen processing and presentation, and to realize that there are two separate intracellular pathways that regulate antigen recognition by T cells (for review see [3]). The understanding that there is an "endogenous pathway" and an "exogenous pathway" of antigen processing and presentation actually required another decade. Therefore, only within the past several years has it become apparent that intracellular infections, especially those due to viruses, require that the viral proteins be synthesized *inside the cell* and then processed into short peptides and loaded onto HLA molecules encoded by the Major Histocompatibility Complex (MHC) Class I genes. Thus, if gp120 or other viral proteins are administered as vaccines, they will not be processed by this pathway, and thus will not activate CD8+ T cells, which are the cells that are primarily responsible for combating intracellular infections.

Recombinant proteins administered as vaccines are processed and presented by the "exogenous pathway" by antigen presenting cells (APCs). This pathway loads antigenic peptides onto HLA molecules encoded by the Class II MHC gene region and ultimately activate CD4+ "helper" T cells. These cells then can "help" the generation of antibodies by B cells and plasma cells, but as noted above, the viral envelope has already thwarted this avenue of defense. Accordingly, the "quick fix" envisioned by early virologists was doomed from the beginning.

Cytokines and the Cell-Mediated Immune (CMI) Response

1983 was also the year that interleukin 2 (IL2) became the first interleukin molecule to be purified to homogeneity [9], cloned and sequenced [10]. Soon thereafter it was demonstrated that the rapid T cell proliferation that occurs *in vitro* after activation with mitogens and antigens is dependent upon the production and action of IL2 by the antigen-selected T cells [11]. However, it wasn't until 1998 that it was possible to demonstrate by *in vivo* experiments that viral antigen-activated T cells undergo a similar rapid and massive proliferative expansion [12–15]. As well, detailed experiments only within the past few years have revealed the crucial role of antiviral cytokines secreted by CD8+ CTL in curtailing viral replication, such as interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α), as a result of advances in flow cytometry and the detection of intracellular cytokines using monoclonal antibodies [16,17].

Successful Vaccines Against Viruses

But what about all the vaccines against all of the viruses that cause the acute infectious diseases of childhood, e.g. poliovirus, measles virus, mumps virus, Rubella virus, chicken pox virus etc., etc.? All of these vaccines were developed empirically in the '50s and '60s before CMI was known about, and almost all of the successful vaccines that have been generated are live attenuated viruses. The key words here are ***live*** and ***attenuated***. Since these viruses are alive, they establish an infection in the cells of the vaccinee. Consequently, the viruses replicate inside the host's cells. This serves to markedly amplify the antigen "dose". As well, while the viruses replicate, their proteins are processed by the endogenous pathway and presented on the

cell surface bound to Class I HLA molecules, thereby activating CD8+ cytolytic T cells (CTL).

Simultaneously, because the infected cells produce mature virions that exit the cells, these virions are opsonized by plasma proteins, and then taken up by phagocytic antigen presenting cells (APCs, macrophages and dendritic cells), which digest the virions, process their proteins to short peptides, and then load them onto HLA Class II molecules. These viral peptide-Class II HLA complexes expressed on the surface of the APCs then activate CD4+ T cells. CD4+ T cells are professional "helpers", and they function to promote both antibody formation by B cells/plasma cells as well as to promote the proliferation and function of CTLs. They do so by expressing "helper molecules" on their cell surface, and as well, as secreted helper molecules (cytokines or interleukins). For example, it turns out, that during an immune response ~80% of the IL2 produced is made by CD4+ helper T cells, whereas CD8+ T cells make only ~20% of the IL2 produced [18]. Therefore, the magnitude of expansion of the number of virus-reactive CD8+ CTLs is highly dependent on CD4+ helper T cells.

The other key word is attenuate. Early on, Albert Sabin found that he could attenuate poliovirus by passaging the virus multiple times in cell cultures. Now we know that this process allowed for the accumulation of many mutations in the viral genome. However, because the selection *in vitro* was governed by viral replication, mutant viruses were derived that had retained their capacity to replicate, a desirable characteristic, but somehow mysteriously they lost their capacity to cause disease, or virulence. Therefore upon inoculation, these attenuated vaccines infect host cells and replicate transiently, thereby amplifying the amounts of viral antigens produced, and thus stimulating a very strong cell-mediated immune (CMI) response. This CMI recognizes and responds to the local infection at the site of inoculation, eradicating the viral vaccine, and leaving behind an expanded population of memory CD4+ and CD8+ T cells that confer life-long protective immunity.

There is one risk to attenuated viral vaccines. If the host is immunocompromised, there is a danger that the host immune response cannot eradicate the local viral vaccine infection. This can result in disseminated "vaccinosis", and disease caused by a systemic infection of the virus comprising the vaccine. The best example of this danger occurs after vaccination for smallpox virus with the cowpox virus, termed vaccinia, which was first described by Jenner [4]. A disseminated vaccinia infection can lead to encephalitis and death. This has recently become an issue, as the Bush Administration has proposed to vaccinate ~500,000 health care workers as a precaution against a possible bio-terrorist attack. Since the cowpox vaccine replicates transiently in a healthy vaccinee, these individuals are contagious for ~2–3 weeks. Accordingly, with ~1 million HIV-infected individuals in the U.S., there is a significant risk of transmission of vaccinia from the vaccinated health care workers to the "at-risk" population of HIV+ individuals.

Accordingly, because of safety concerns live attenuated HIV vaccines have been ruled out. In addition, all of the HIV vaccines under development have been chosen so that the viruses used as "vectors" are crippled and are ***replication defective***. Thus, "naked" DNA vaccines derived from bacterial viruses (plasmids) cannot replicate in human cells. As well, vaccines produced in viral vectors derived from canarypox virus, fowlpox virus, adenovirus, alpha virus etc. have been purposely chosen because these viruses are replication-defective in human cells. Consequently, one advantage of using live viruses as vectors for vaccines is lost. The vaccine virus cannot replicate in the host tissues, even transiently, so that the antigen dose is orders of magnitude less than can be achieved by a viral vaccine that can replicate.

The caveat is that the attenuated, live viral vectors can still infect host cells, so that they deliver the virally-encoded genes into the cell, and the expressed viral gene products are processed into short peptides and presented on the cell surface bound to HLA Class I molecules that can stimulate the recognition and response of CD8+ CTLs. Even so, with the loss of vaccine replication, all of the current HIV vaccines in development are relatively weak immunogens as determined by measurements of both humoral and CMI. They are relatively weak vaccines because they do not replicate so that the antigen dose is limited. Also they are weak immunogens because they do not produce mature virions that can be taken up by APCs. Therefore, viral peptides are not processed via the "exogenous" Class II HLA pathway, activating CD4+ T helper cells. Thus, without help the CD8+ T cell proliferative response is blunted and meager, as is the humoral antibody response.

Protection From Disease instead of Prevention of Infection

Traditionally, vaccine-induced generation of high titers of neutralizing antibodies was found to prevent infection upon exposure to the wild-type virus in the field, and this is the way new vaccines are traditionally tested. The vaccine doses and regimens are first tested in normal volunteers for their capacity to invoke high titers of neutralizing antibodies. Then, the vaccine and placebo are introduced into a population where the incidence of infection is high, and the frequencies of infections are compared in the vaccinated group vs. the placebo control group. This approach requires a reasonably high incidence of infection in the endogenous population, and a reasonable rate of

infection, so that the trial can be conducted in a reasonable time frame. However, even in the best of circumstances, usually several thousand volunteers and several years are required to acquire definitive data as to whether a vaccine will work, and how well it works, i.e. whether it confers complete protection from infection, or only partially effective, affording protection for a fraction of vaccinees compared with the incidence in the placebo control group.

If a vaccine fails to prevent infection, it can still be quite effective if it can be shown to prevent the disease caused by the wild-type virus. Actually, for most of the present vaccines, tests for the persistence of viral genome in the host were not available when the original vaccines were developed, so that whether the vaccine prevents infection or protects against development of disease remains unknown.

The Simian Immunodeficiency Virus (SIV) Model

SIV infection of Rhesus macaques has been found to result in an immunodeficiency syndrome very similar to the AIDS caused by HIV infection of humans. In hopes of creating an animal model that would mimic the human infection, Reiman and Letvin and their co-workers generated chimeric simian/human immunodeficiency viruses (SHIV) [19]. Viruses composed of SIVmac239 expressing HIV-1 *env* and associated auxiliary HIV-1 genes *tat*, *vpu*, and *rev*, is designated SHIV89.6P. One of the major differences between the infections of macaques by SHIV89.6P vs. HIV infections of humans is the rate of development of AIDS, which occurs after just a few months in the SHIV-infected macaque, compared with several years in HIV-infected humans. Therefore, the SHIV-induced disease is an acute infection compared with the chronic infection caused by HIV. From the standpoint of a vaccine model, this aspect of SIV infection works to the advantage of the investigator. SHIV vaccine clinical trials can be conducted over a much shorter time interval than would be the case if the macaque infection model had a similar time frame as the human infection. In addition, an obvious advantage to the SHIV model is that experiments can be conducted where all of the vaccinated animals can be challenged with wild-type virus simultaneously, and virologic and immunologic parameters can be monitored carefully.

Using this model, Dan Barouch and Norm Letvin and their co-workers have pioneered the SHIV model to test vaccines [20,21]. In several recent reports they have found that it is possible to protect Rhesus macaques from the development of AIDS, but it has not yet been possible to demonstrate that vaccination can prevent infection by SHIV. In experiments testing naked DNA vaccines comprised of the envelope from HIV and the SIV Group-specific Antigen Genes (*gag*) they found that when given alone, the naked DNA vaccine was a weak immunogen. By comparison, there was a readily detectable CMI response when IL2 was administered together with the first two doses of vaccine in the form of a chimeric IL2-Ig protein, which functions to prolong it's plasma half-life, or as the gene encoding the IL2-Ig chimera [20]. As well, after challenge with SHIV89.6P, all of the animals that received the control, empty vector, or naked DNA vaccines alone, developed persistent viremia, falling CD4+ T cell counts, and eventually succumbed to AIDS. By comparison, after challenging the animals that received the DNA vaccines given together with IL2-Ig, there were potent secondary CTL responses, the CD4+ T cell concentrations remained stable and normal, *in vitro* CD4+ T cell SHIV-specific proliferative responses were maintained, the peak plasma SHIV concentrations were ~10-fold lower than in animals that received either no vaccine or naked DNA vaccine alone, and the eventual viral "set points" were < 1,000 copies/mL. Even more notable, none of the 8 animals that received the DNA vaccine + IL2-Ig had evidence of clinical disease by day 140 (5 months) after viral challenge, while half of the controls had died.

These experiments thus provided "proof of concept" that it is possible to boost immune recognition and reactivity to SHIV infection by immunization with naked DNA vaccines, and furthermore they pointed the way to the use of cytokines as adjuvants, to boost the poorly immunogenic non-replicative vaccines. Subsequently, Shiver and co-workers reported success with naked DNA vaccines combined with modified vaccinia Ankara (MVA) virus (which is replication incompetent in mammalian cells) and a replication incompetent adenovirus type 5 (Ad5) vector [22]. These investigators did not use IL2 or other cytokines as adjuvants, but they also did not achieve the same degree of immune reactivity as reported by the Barouch team.

More recently, Barouch and co-workers reported that one of the 8 animals that were virus and disease-free 5 months after virus challenge had subsequently suffered a viral relapse at week 24 and succumbed to AIDS at week 52 [23]. Moreover, they were able to detect that one "immunodominant" CTL epitope had undergone a mutation, thereby suggesting that the immunosurveillance is ongoing in these vaccinated and challenged animals, and that escape from immune recognition is a danger. Even so, 7/8 animals remain virus- and disease-free > 2 years after virus challenge.

Very recently, Willey and co-workers reported on experiments using the SHIV model and recombinant vaccinia virus plus chemically inactivated SIV and HIV viral particles as vaccines [24]. Macaques were immunized with the recombinant vaccinia vaccines on weeks 0 and 8, and then

followed with injections of the viral particles on weeks 20 and 28. Following virus challenge on week 46, all control animals experienced a rapid and complete loss of CD4+ T cells, sustained high plasma virus concentrations, and developed AIDS by 17 to 21 weeks. By comparison, although all the vaccinated monkeys became infected, they displayed reduced peak viremia, had no significant loss of CD4+ T cells, and have remained healthy for more than 15 months post infection. Even so, these animals still have detectable viremia, albeit at low concentrations, ~1,000 mol/mL.

All of these experiments in the experimental macaque model system point towards the capacity of the host to contain the virus after infection, and they indicate that it is possible to boost immune reactivity prophylactically with various vaccines and adjuvants. However, the SHIV-macaque model is still only a model [25], so that these principles must be transferred to the human, and then tested as rapidly as possible to discern how best to stimulate immunity to HIV.

Testing Vaccine Candidates in Humans: Ethical and Practical Issues

Moving from monkeys to man is a big step. Recently, an article in *The New Yorker* entitled "The Vaccine" very aptly posed the question, "*Has the race to save Africa from AIDS put Western science at odds with Western ethics?*" [26]. This article details the difficulties in testing a vaccine candidate for efficacy in the third world, where cultural beliefs and superstitions are compounded by political instability and the lack of a medical infrastructure. The article quotes Nobel Laureate and head of the AIDS Vaccine Initiative, David Baltimore, who has said repeatedly that this battle will take many years, a lot of money and many people.

The problem of convincing an uneducated and suspicious populace to participate in an experiment to test an unproven vaccine for the capacity to prevent HIV infection is underscored by a statement from one African leader who said that it was easier to convince people of his country to submit to poliovirus vaccination, because it had already been shown to be efficacious in the "first world".

At this point, HIV vaccines have been tested in normal human volunteers for more than a decade, and there are plans to begin large-scale prophylactic vaccine trials soon. For example, Aventis Pasteur has developed a candidate vaccine from canarypox virus that they plan to test in a placebo-controlled trial in Thailand on 16,000 normal, HIV-negative volunteers. They estimate that the trial will proceed for at least 4 years before any data will become available as to the efficacy of their vaccine [27].

An additional difficulty of testing vaccines vs. testing antiviral drugs relates to the nature of the immune system and immunologic memory. An individual can participate in multiple successive trials testing antivirals after a suitable washout period to ensure that there is no longer any drug remaining before administering a new agent. As well, because the antiviral drugs target the virus, instead of the host, there is less concern that a prior exposure will have altered the host. However, a vaccine targets the immune system, and the immune system remembers past exposures. Thus, an individual can ideally only volunteer for one vaccine trial. If the individuals of a community have already participated in a vaccine trial, their immune systems have been primed to the antigens contained in the vaccine and they will have an anamnestic response rather than a primary response to a new vaccine that contains the same or similar antigens.

Finally, ethicists are concerned that the volunteers in a vaccine trial in the third world should be treated identically as would volunteers from the first world. Thus, there is a debate as to whether volunteers in a vaccine trial who receive placebo, and who subsequently become infected with HIV be offered the expensive, life-saving antiviral medications that are available in the first world, but not common practice in their society. Who should pay for these drugs? As well, is it ethical to administer these drugs to the vaccine volunteers but not to individuals of the society who have not volunteered for the trial?

The Solution: Test Candidate Vaccines First in the "First" World in HIV+ Volunteers

Conventional wisdom has maintained that once HIV infection becomes chronic, i.e. once the virus invades the host and establishes itself in susceptible CD4+ T cells, the immune system is irrevocably compromised [28]. In favor of this viewpoint is the fact that antiviral drugs are not curative. Thus, even though antivirals can reduce plasma HIV concentrations to undetectable levels for months and even years, if the drugs are discontinued, viremia recurs within a few weeks, and the immune system still cannot prevent the relapse [29], even though the antivirals have reduced the total viral burden to a tiny fraction of cells, ~1 infected cell per million CD4+ T cells [30].

Against this conventional wisdom are our studies in which we treated chronically infected subjects with antivirals and IL2 for at least 3 months, following which we discontinued the antivirals, continued the IL2 administration and then monitored the plasma HIV concentration and the concentration of circulating lymphocytes [31] (and unpublished data). Thus far, in 15 subjects we have found a characteristic relapse of viremia within ~2 1/2 weeks, then a rapid increase in HIV concentration for ~2 weeks (mean doubling time 1.6 days) to a

peak viral concentration of ~250,000 HIV RNA mol/mL. Subsequently, the circulating CD8+ T cell concentration doubled and the plasma HIV concentration declined ~10-fold to a mean "trough" or viral "set point" concentration of ~25,000 HIV RNA mol/mL. Moreover, the rate of decline of the plasma virus concentration correlated with the magnitude of the increase in the CD8+ T cell concentration.

These findings are reminiscent of the changes in viral and lymphocyte dynamics that occur after a primary infection. However, they are more consistent with an anamnestic immune response, which would be expected of a "primed" host. Thus, the rate of viral increase is ~4–5-fold slower than in a primary infection, and the peak viral concentration is ~100-fold lower than in a primary infection [32]. Moreover, the rate of decline of the plasma virus concentration, which has been attributed to CD8+ T cells in the macaque model system, is just as rapid as observed after the administration of antivirals (i.e. t1/2 = 2–3 days) [33,34].

Given these data, one can readily see how the viral and lymphocyte dynamics after a brief 8–12 week discontinuation of antivirals can be used to test the capacity of the immune system to recognize and respond to each individual's endogenous virus. Accordingly, we have termed this treatment interruption as a "Diagnostic Treatment Interruption" (DTI) to designate that it is not a therapeutic manipulation as a "Structured Treatment Interruption" (STI) has come to denote. Moreover, a DTI is diagnostic of the capacity of the immune system to recognize, react and control the virus in the absence of the suppressive antiviral drugs [18,35].

The advantage of a DTI for a clinical trial design to test HIV vaccines is obvious. The determination of the plasma HIV concentration is now a very sensitive, reproducible and accurate assay. In addition, because the viral relapse occurs so rapidly, within ~2–3 weeks, the outcome of the vaccination can be determined in a very short time interval. In essence, this clinical trial design is similar to the design used in cancer therapy, where chemotherapy is given until the cancer is no longer evident, and then a relapse rate of the return of detectable tumors is monitored after the chemotherapy is withdrawn. The additional advantage is that the viral load assay is analogous to monitoring a biochemical tumor maker such as the PSA test is used to diagnose the relapse of prostate cancer, without waiting for the return of grossly detectable tumor.

The other obvious advantage of the use of a DTI to test the efficacy of HIV vaccines and immune-based therapies (IBTs) is that it tests directly the *antiviral capacity* of the immune system, and does not rely on the use of assays of the immune system function that may, or may not, correlate with an antiviral response. For example, measurements of lymphocyte proliferation assays or cytotoxicity assays, or ELISPOTs or flow cytometry of antigen-activated cells only give a measurement of the antiviral *potential* of the immune system and do not actually measure its antiviral *capacity*.

Accordingly, it is possible to test the various vaccines in development, as well the various doses and regimens, with and without cytokines in the "first" world, where we have available all the infrastructures of clinical medicine and basic science, as well as an educated and motivated population of volunteers. If a particular vaccine, dose and regimen tests superior in therapeutic vaccine trials, then this formula should be the one taken to prophylactic tests in the "third" world.

One last aspect of vaccine testing to discuss is the tradition of a placebo control. In cancer chemotherapy trials, a placebo control is no longer used or considered to be ethical. Thus, "standard therapy" serves as the control group, with which an experimental group is compared. Accordingly, before testing new vaccines in the third world, at least two promising vaccines, doses and regimens should first be identified in the first world in therapeutic trials, and then compared with one another in the third world in prophylactic trials. If one vaccine and regimen is found superior to the other, it should then be used as the "standard vaccine" for comparison with an experimental vaccine in the next trial. This approach should make the idea of volunteering for a vaccine trial in the third world much more palatable, and therefore decidedly more easily accomplished by first and third world scientists and physicians, working together.

Conclusions

Given the understanding of how the immune system functions, combined with the ability to rapidly and definitively test therapeutic vaccines in HIV+ volunteers, a rational and successful approach to testing therapeutic and prophylactic HIV vaccines is now within reach. However, the scientific, medical and HIV-infected communities of the first world must mobilize to perform the necessary crucial clinical research before vaccines and immunotherapies can be applied effectively worldwide as rapidly as possible.

Competing interests

None declared.

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